PROTEIN ARGININE METHYLTRANSFERASE 5 (PRMT5) DEGRADATION / DISRUPTION COMPOUNDS AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 62/634,039, filed on Feb. 22, 2018. The entire contents of the foregoing are incorporated herein by reference.

TECHNICAL FIELD

[0002] This disclosure relates to bivalent compounds (e.g., bi-functional compounds, e.g., bi functional small molecule compounds) which degrade and/or disrupt protein arginine methyltransferase 5 (PRMT5), compositions comprising one or more of the bivalent compounds, and methods of use thereof for the treatment of PRMT5-mediated diseases in a subject in need thereof. The disclosure also relates to methods for designing such bivalent compounds.

BACKGROUND OF THE INVENTION

[0003] Protein arginine methyltransferases (PRMTs) catalyze an important post-translational modification in eukaryotic cells, arginine methylation. Significant efforts have been spent attempting to develop small molecule inhibitors of the methyltransferase activity of protein arginine methyltransferace 5 (PRMT5) because overexpression of PRMT5 is associated with several human malignancies, including lymphomas, melanoma, adenocarcinoma, pancreas, prostate, lung cancer, breast cancer, colorectal, and ovarian cancer. PRMT5 is one of nine protein arginine methyltransferases that transfer the methyl group from the cofactor S-5'-adenosyl-L-methionine (SAM) to arginine residues of a variety of histone and non-histone proteins. Methylation of protonated arginine guanidium moieties (positively charged at physiological conditions) increases their bulkiness and alters their charge distribution, hydrophobicity, and hydrogen bond formation potential, thus affecting their protein- and nucleic acid-binding activity and ultimately their physiological function (Wei et al., 2014). Dysregulation of PRMTs has been linked to a variety of human diseases, such as pulmonary diseases, cardiovascular disease, diabetes, renal disease, Huntington's disease, Alzheimer's disease, asthma, and verities of cancer (Hu et al., 2016).

[0004] Nine PRMTs have been identified. Based on their product specificity, they are grouped into three categories, type I, type II and type III. Type I PRMTs (PRMT1-4, PRMT6 and PRMT5) catalyze arginine mono- and asymmetric dimethylation. Type II PRMTs (PRMT5 and PRMT5) catalyze arginine mono- and symmetric dimethylation. Type III PRMT (PRMT7) catalyzes arginine monomethylation only (Kaniskan et al., 2015). Protein arginine methyltransferase 5 (PRMT5) is the predominate type II PRMT and the major enzyme for arginine symmetric dimethylation.

[0005] PRMT5 methylates a variety of histone substrates in vivo, including H2AR3, H4R3, H3R2, and H3R8, which are associated with transcriptional regulatory processes. PRMT5 also methylates many non-histone proteins, including SmD3, NF-κB, p53, E2F-1, Raf, and RPS 10. Through the regulation of these non-histone targets, PRMT5 plays important roles in processes including RNA splicing, transcription, signaling pathway, and ribosome biogenesis. The substrate specificity of PRMT5 is regulated by its binding partners, including Blimp1, RioK1, pICLn, MBD/NuRD, and MEP50. The most common PRMT5 partner is MEP50, a member of the WD40 family of proteins, which is required for PRMT5 enzymatic activity and is likely present in every PRMT5-containing complex in vivo.

[0006] However, traditional catalytic inhibition of PRMT5 has not been an optimal solution for treating PRMT5 overexpression. First, cancer cells frequently develop resistance to small molecule inhibitors through mutations in the active site that overcome pharmacological inhibition. Second, most proteins have functions in addition to the (catalytic) activity targeted by small molecule inhibitors. For example, methyltransferases form complexes with other proteins through protein-protein interactions, and bind DNA directly at transcriptional promoter sites. Studies have shown that treating cancer cells with the enzymatic inhibitor EPZ015666 alone failed to optimally inhibit cancer cell proliferation. (Jin, 2016; Kryukov, 2016).

[0007] PRMT5 overexpression has been associated with multiple human malignancies, including lymphomas, melanoma, adenocarcinoma, pancreatic cancer, prostate cancer, lung cancer, breast cancer, colorectal cancer, and ovarian cancer. For example, overexpression of PRMT5 has been reported in human chronic myelogenous leukemia (CML) leukemia stem cells (LSCs). PRMT5 knockdown or inhibition dramatically prolonged survival in a murine model of BCR-ABL-driven CML and impaired the in vivo self-renewal capacity of transplanted CML LSCs (Jin et al., 2016). PRMT5 expression levels are significantly higher in gastric cancer (GC) tissues than the corresponding adjacent normal tissues. Knockdown of PRMT5 decreased the proliferation, invasion and migration of a GC cell line (Kanda et al., 2016). PRMT5 overexpression in patient multiple myeloma (MM) cells is associated with decreased progression-free survival and overall survival. Genetic knockdown of PRMT5 or inhibition of PRMT5 significantly inhibited the growth of patient MM cells (Gulla et al., 2017). PRMT5 promotes prostate cancer cell growth through androgen receptor (AR) upregulation. Knockdown of PRMT5 or inhibition of PRMT5 decreases the AR expression and suppresses the proliferation of AR-positive, but not AR-negative, prostate cancer cells (Deng et al., 2017). PRMT5 has been reported as a key mediator of glioblastoma (GBM) growth. PRMT5 knockdown or inhibition potently suppressed in vivo GBM tumors, including patient-derived xenografts (Braun et al., 2017). PRMT5 overexpression in hepatocellular carcinoma (HCC) tissues is associated with advanced disease stage and adverse prognosis. PRMT5 knockdown significantly decreased the proliferation, invasion, and migration of HCC cell lines (Shimizu et al., 2017). PRMT5 is highly expressed in pancreatic ductal adenocarcinoma (PDAC) and colorectal cancer (CRC). PRMT5 promotes cancer progression through the activation of NF-κB, while shRNA knockdown had opposite effect (Prabhu et al., 2017).

[0008] Significant efforts have been made to the development of therapeutics capable of inhibiting the methyltransferase activity of PRMT5. A number of PRMT5 inhibitors have been published, including EPZ015666, GSK591, GSK3326595 (EPZ015938), BLL-1, HLCL-61, and LLY-283 and PF-06855800. Several compounds including